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(12) (19) (CA) **Demande-Application**

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(54) **PRODROGUES ANTICANCER A ACTION DOUBLE**
(54) **DUAL ACTION ANTICANCER PRODRUGS**

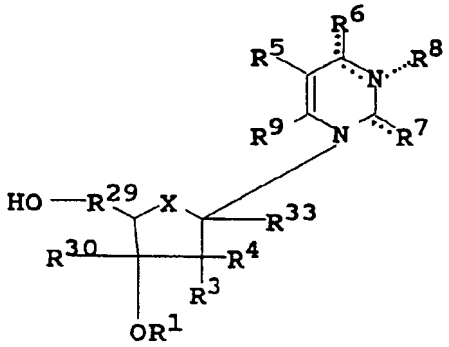
(57) This invention is concerned with novel dual acting anti-tumor drugs. These dual acting anti-tumor drugs comprise at least two moieties. One of the moieties can be an agent that stimulates the differentiation of tumor cells. Examples of the moiety includes butanoyl and retinoyl groups. Another moiety is a hydroxy-containing anti-tumor agent. Examples of the hydroxy-containing anti-tumor agent are nucleoside analogs, steroids having anti-tumor activity and anthracyclines. Also disclosed, are methods of using the dual acting anti-tumor drugs to prevent or treat a tumor and a process of making these drugs.

ABSTRACT

This invention is concerned with novel dual acting anti-tumor drugs. These dual acting anti-tumor drugs comprise at least two moieties. One of the moieties can be an agent that stimulates the differentiation of tumor cells. Examples of the moiety includes butanoyl and retinoyl groups. Another moiety is a hydroxy-containing anti-tumor agent. Examples of the hydroxy-containing anti-tumor agent are nucleoside analogs, steroids having anti-tumor activity and anthracyclines. Also disclosed, are methods of using the dual acting anti-tumor drugs to prevent or treat a tumor and a process of making these drugs.

Claims

1. A compound of formula I,



I

wherein ..... is a single bond or a double bond;

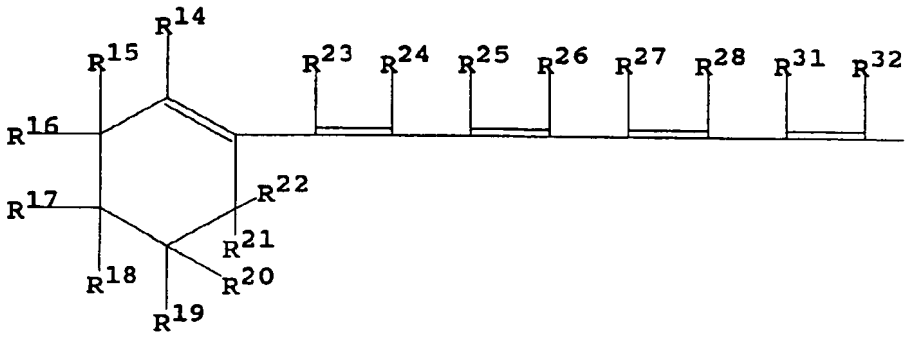
X is O, S, SO, SO_2, CH_2 or $-CH(CH_3)-$;

R^1 and R^2 are independently H, RC(O)- or $(R^{10})(R^{11})P(O)-$, wherein R^1 and R^2 cannot both be H;

R is:

(1) C_1-C_7 alkyl or C_2-C_7 alkenyl optionally substituted by a radical selected from the group consisting of OH, SH, $-NR^{12}R^{13}$, F, Cl, Br and I, wherein R^{12} and R^{13} are independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl, or R^{12} and R^{13} together with the nitrogen atom attached form an optionally substituted 5- or 6-membered heterocyclic, wherein 1, 2 or 3 ring carbon atoms of said heterocyclic are optionally replaced by N, O or S; or

(2) a radical of formula II,



II

R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{30}, R^{31}, R^{32} and R^{33} are independently H, OH, SH, $-NR^{12}R^{13}$, F, Cl, Br, I, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_7 alkylcarbonyl, C_2-C_7 alkylthiocarbonyl, C_3-C_7 alkenylcarbonyl, C_3-C_7 alkenylthiocarbonyl, benzoyl, thiobenzoyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_2-C_7 acyloxy, C_2-C_7 alkylthiocarbonyloxy, C_2-C_7 alkenylcarbonyloxy, C_2-C_7 alkenylthiocarbonyloxy, C_3-C_6 cycloalkyl, phenyl or naphthyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_7 alkylcarbonyl, C_2-C_7 alkylthiocarbonyl, C_3-C_7 alkenylcarbonyl, C_3-C_7 alkenylthiocarbonyl, benzoyl, thiobenzoyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_2-C_7 acyloxy, C_2-C_7 alkylthiocarbonyloxy, C_2-C_7 alkenylcarbonyloxy, C_2-C_7 alkenylthiocarbonyloxy, C_3-C_6 cycloalkyl, phenyl and naphthyl are optionally substituted;

wherein R^8 does not exist when ⋯ is a double bond between N at the 3-position and C at the 4-position of the pyrimidinyl ring;

wherein R^{10} and R^{11} cannot both be H;

wherein R^{14} and R^{15}, together with the carbon atoms attached, may form an optionally substituted C_3-C_8 cycloalkyl;

wherein R^{18} and R^{19}, together with the carbon atoms attached, may form an optionally substituted C_3-C_8 cycloalkyl or optionally substituted phenyl;

wherein R^{16} and R^{17}, together with the carbon atoms attached, may form an optionally substituted C_3-C_8 cycloalkyl or optionally substituted phenyl if R^{14} and R^{15} together do not form the C_3-C_8 cycloalkyl and/or R^{18} and R^{19} together do not form the C_3-C_8 cycloalkyl or phenyl;

wherein R^{20} and R^{21}, together with the carbon atoms attached, may form an optionally substituted C_3-C_8 cycloalkyl or optionally substituted phenyl if R^{18} and R^{19} together do not form the C_3-C_8 cycloalkyl or phenyl;

wherein R^{15} and R^{16}, together with the carbon atom attached, may form an oxo group;

wherein R^{17} and R^{18}, together with the carbon atom attached, may form an oxo group;

wherein R^{19} and R^{20}, together with the carbon atom attached, may form an oxo group;

wherein R^{21} and R^{22}, together with the carbon atom attached, may form an oxo group;

R^6 and R^7 are independently H, OH, SH, O, S, $-NR^{12}R^{13}$, F, Cl, Br, I, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_7 alkylcarbonyl, C_2-C_7 alkylthiocarbonyl, C_3-C_7 alkenylcarbonyl,

C_3-C_7 alkenylthiocarbonyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_2-C_7 acyloxy, C_2-C_7 alkylthiocarbonyloxy, C_2-C_7 alkenylcarbonyloxy, C_2-C_7 alkenylthiocarbonyloxy, C_3-C_6 cycloalkyl, phenyl or naphthyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_7 alkylcarbonyl, C_2-C_7 alkylthiocarbonyl, C_3-C_7 alkenylcarbonyl, C_3-C_7 alkenylthiocarbonyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_2-C_7 acyloxy, C_2-C_7 alkylthiocarbonyloxy, C_2-C_7 alkenylcarbonyloxy, C_2-C_7 alkenylthiocarbonyloxy, C_3-C_6 cycloalkyl, phenyl and naphthyl are optionally substituted; wherein R^6 and R^7 cannot both be H;

R^{29} is methylene optionally substituted by methyl, ethyl, OH, SH, $-NR^{12}R^{13}$, F, Cl, Br or I;

wherein "optionally substituted" means, unless otherwise stated, optionally having attached one to five substituents independently selected from OH, SH, $-NR^{12}R^{13}$, F, Cl, Br or I, wherein no more than three substituents are present if the radically optionally substituted is methyl, acetyl, thioacetyl, methoxy or methylthio;

or a tautomer, stereo isomer, geometric isomer, pharmaceutically acceptable salt, hydrate or solvate thereof.

2. A pharmaceutical composition, which can be used to treat tumors, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

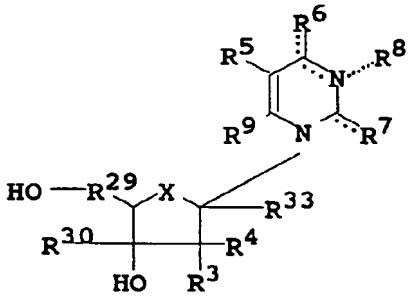
3. A method for treating a tumor in a patient by administering an effective amount of a compound of claim 1 into the patient.

4. The method of claim 3, wherein the tumor is a solid tumor or leukemia.

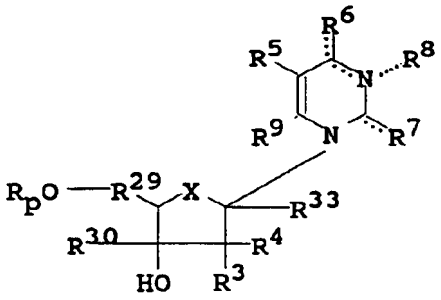
5. The method of claim 4, wherein the tumor is acute promyelocytic leukemia, juvenile chronic myelogenous leukemia, renal cancer, Kaposi's sarcoma, keratoacanthoma, skin cancer, lung cancer, esophageal cancer, cancer of the urinary tract, breast cancer, cervical cancer, squamous cell carcinomas of the head and neck, adenocarcinoma of the gastrointestinal tract, colon cancer, pancreatic tumor, liver tumor, biliary tract tumor, carcinoma of the oropharynx, ovary or prostate, endometrial adenocarcinoma, teratocarcinoma or thyroid carcinoma.

6. A process for making a compound of formula I according to claim 1, comprising the following steps:

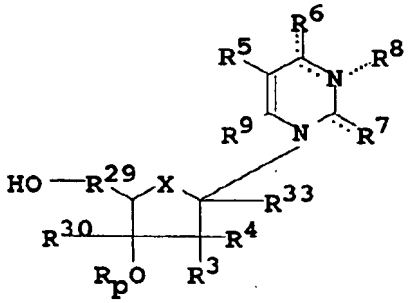
(1) providing an intermediate of formula III, IV or V,



III



IV



V

wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{29}, R^{30} and R^{33} are as defined in claim 1; R_p is a hydroxy protecting group; wherein optional OH groups in R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{29}, R^{30} and R^{33} are protected with hydroxy protecting groups and optional SH groups in R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{29}, R^{30} and R^{33} are protected with sulfydryl protecting groups;

(2a) wherein one of R^1 and R^2 is H, and the remaining R^1 or R^2 is RC(O)-, wherein R is C_1-C_7 alkyl optionally substituted by a radical selected from the group consisting of OH, SH, -$NR^{12}R^{13}$, F, Cl, Br and I, wherein R^{12} and R^{13} are as defined in claim 1; or wherein R is a radical of formula II as defined in claim 1,

reacting the intermediate of formula IV or V with RC(O)Cl or RC(O)-O-C(O)R, optionally followed by removing the protecting groups for the optional hydroxy or sulfydryl groups, to obtain a compound of formula I;

(2b) wherein one of R^1 and R^2 is H and the remaining R^1 or R^2 is $(R^{10})(R^{11})P(O)$-, wherein R^{10} and R^{11} are as defined in claim 1,

reacting the intermediate of formula IV or V with $(R^{10})(R^{11})P(O)Cl$, optionally followed by removing the protecting groups for the optional hydroxy or sulfydryl groups, to obtain a compound of formula I;

(2c) wherein R^1 and R^2 are both RC(O)- with R being either

(i) C_1-C_7 alkyl optionally substituted by a radical selected from the group consisting of OH, SH, -$NR^{12}R^{13}$, F, Cl, Br and I, wherein R^{12} and R^{13} are as defined in claim 1, or

(ii) a radical of formula II as defined in claim 1;

reacting the intermediate of formula III with RC(O)Cl or RC(O)-O-C(O)R, optionally

followed by removing the protecting groups for the optional hydroxy or sulfydryl groups, to obtain a compound of formula I;

(2d) wherein R^1 and R^2 are both $(R^{10})(R^{11})P(O)$-, wherein R^{10} and R^{11} are as defined in claim 1;

reacting the intermediate of formula III with $(R^{10})(R^{11})P(O)Cl$, optionally followed by removing the protecting groups for the optional hydroxy or sulfydryl groups, to obtain a compound of formula I; or

(2e) wherein neither R^1 nor R^2 is H, and R^1 and R^2 are RC(O)- or $(R^{10})(R^{11})P(O)$- with R^1 and R^2 being different;

(i) reacting the intermediate of formula IV or V with starting compound A, which starting compound A is RC(O)Cl, RC(O)-O-C(O)R or $(R^{10})(R^{11})P(O)Cl$, wherein R, R^{10} and R^{11} are as defined in claim 1 to obtain a product of step (i);

(ii) removing the hydroxy protecting group(s) in the product of step (i) to obtain a product of step (ii);

(iii) reacting the product of step (ii) with starting compound B, which starting compound B is different from starting compound A, wherein said starting compound B is RC(O)Cl, RC(O)-O-C(O)R or $(R^{10})(R^{11})P(O)Cl$ to obtain a product of step (iii);

(iv) removing the optional sulfydryl protecting groups to obtain a compound of formula I;

and thereafter converting the compound of formula I into a pharmaceutically acceptable

salt, hydrate or solvate thereof if desired.